

Electrophysiologic Disorders

Use of Global Atrial Fibrillation Organization to Optimize the Success of Burst Pace Termination

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OBJECTIVES	The purpose of this study was to determine if burst atrial pacing would have an effect on terminating atrial fibrillation.
BACKGROUND	We hypothesized that frequency domain analysis of a filtered wide bipolar atrial electrogram describes the global organization of atrial fibrillation (AF) and should vary over time. Timing burst pacing to periods of high organization of AF should promote regional atrial conduction block and terminate AF.
METHODS	Nine dogs were conditioned with rapid atrial pacing for 48 h. Electrogram recordings were made from a wide right atrium (RA) to left atrium (LA) bipole and digitally filtered. A fast-Fourier transform was performed every 0.5 s on a sliding 2-s window, and the organization index (OI) was calculated as a ratio of the area of the first four harmonic peaks to the total power of the spectrum. Organization indexes >0.5 indicated more organized AF activity. Right atrium and LA burst pacing (burst) (cycle length 50 ms, 9.9 ms, 9.9 mA, 1 to 4 s) was performed through decapolar catheters. Burst was either random or synchronized to OI >0.5 .
RESULTS	Burst termination was attempted 1,814 times (889 OI sync, 925 random) and succeeded in seven of nine dogs. Burst had an overall success rate of 11.1% versus 6.3% for random ($p < 0.0003$). Batrial pacing had the highest efficacy for terminating AF, with a success rate of 16.5% for OI sync versus 8.2% for random ($p < 0.0001$).
CONCLUSIONS	Timing the delivery of the burst pace when the OI is >0.5 increases the efficacy of burst pace termination of AF. Batrial pacing is more effective than either RA or LA pacing alone. (J Am Coll Cardiol 2002;40:1831–40) © 2002 by the American College of Cardiology Foundation

Atrial flutter can be successfully entrained and terminated with atrial overdrive pacing (1–10). Atrial fibrillation (AF) in animals can be regionally entrained for short periods (11,12). Recently, it has been shown that AF can be regionally entrained in humans (13–15). Even though regional entrainment of AF has been demonstrated, termination of AF during these conditions has not been successful. Overdrive atrial pacing could produce regional atrial refractoriness and conduction block in regions of excitable gap, and possibly block the propagation of reentrant wavelets. A high-frequency burst protocol has been implemented into atrial implantable defibrillators as a therapeutic option for termination of AF, but has had limited success (16–18).

Recently, we have developed a new metric for quantifying the organization of AF with frequency domain analysis, termed the organization index (OI) (19,20). Atrial fibrillation varies in spatiotemporal organization and has periods of higher organization where the AF is more “flutterlike.” There is a decrease in atrial defibrillation thresholds in

canines when shocks are timed to periods of measured high AF organization, as determined by the OI. There is evidence that the mechanism of AF in the animal model used in this study is reentrant wavelets (11,12,21). The number of wavelets circulating in the atria probably varies with changing global and regional refractoriness, and is inversely related to the spatiotemporal organization and regions of excitable gaps. A pacing impulse that occurs during the excitable gap may capture the atria and terminate AF. It was hypothesized that if the delivery of burst rapid atrial pacing were timed to periods of measured high AF organization when a longer excitable gap may exist, the efficacy of burst pace termination of AF should improve.

Finally, several studies have shown that there are differences in the electrophysiologic properties in the left atrium (LA) and right atrium (RA) (21–25). These differences have been shown to lead to differences in signal conduction between the atria and to a gradient in dominant frequencies during AF in these models (24–26). This in turn may lead to differences in AF organization between the LA and RA, which can influence how the AF is affected by the burst pacing, depending on the pacing site. We hypothesized that the pacing site would play a role in the efficacy of the termination of AF with burst pacing.

The purpose of this study was to determine if burst atrial

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Abbreviations and Acronyms

AF	= atrial fibrillation
CL	= cycle length
EG	= electrogram
FFT	= fast-Fourier transform
LA	= left atrium
OI	= organization index
RA	= right atrium
SR	= sinus rhythm

pacing would have an effect on terminating AF, if timing the delivery of the burst to a high OI would improve the success rate of burst pace termination, and the best site and duration of burst pace delivery.

METHODS

All animal protocols were reviewed and approved by the Animal Research Committee at the University of Virginia Health System, conformed to the guidelines published in the "Position of the American Heart Association on Research Animal Use," and were conducted with the assistance/supervision of the Animal Resources Department veterinary staff.

Animal preparation. Nine mongrel dogs weighing 31.9 ± 2.7 kg were induced with sodium pentothal (0.25 mg/kg) and intubated, and isoflurane (0.5% to 1.5%) or halothane (0.5% to 1.5%) were used for maintenance anesthesia. The animals were conditioned with 48 h of rapid atrial pacing as previously described (19). The right neck and interscapular regions were sterilely prepped and draped. An active fixation atrial "J" permanent pacemaker lead (Medtronic Inc., Minneapolis, Minnesota) was introduced into the right jugular vein through a cut-down incision, and was advanced into the right atrial appendage under fluoroscopic guidance. Pacing parameters were tested and the lead position was fixed at the venous entry point. A pacemaker pocket was created between the scapulae, and the lead was tunneled to the pocket. The lead was connected to a specially modified Teletronics (Englewood, Colorado) unipolar implantable pulse generator and appropriate atrial pacing was confirmed. The wounds were repaired and the animals returned to the vivarium. The pacemakers were programmed to a rate of 640 beats/min, a pulse width of 0.5 ms, and an output of 5 V.

After 48 h of rapid atrial pacing, the animals were anesthetized and the femoral vessels were accessed via cut-down incision. Two transseptal catheterizations were performed using a Brockenbrough needle and two 9.5F 80 cm sheaths. Decapolar catheters with 10 mm spacing between each bipole were placed in the right and left appendages for electrogram (EG) recording and for burst pacing. Coil electrode catheters were placed contiguous to right and left atrial free walls to create an interatrial bipole EG. These catheters were specially constructed 7F catheters with stainless steel defibrillation coils (Boston Scientific

Corporation) having a surface area of 3.64 cm^2 . The dogs were euthanized with a barbiturate overdose at the completion of the protocol.

Signal processing and frequency domain analysis. The wide bipole signal obtained from the coil electrode catheters (Fig. 1) was acquired and analyzed as described previously (20). Briefly, the signal was digitized at 1,000 Hz using a 486 66 MHz computer with an AT-DSP2200 data acquisition card (National Instruments Corporation, Austin, Texas) programmed in Turbo C++. An ideal QRS was determined by averaging 100 QRS complexes. This ideal QRS was then subtracted from each individual QRS complex in the signal. The resulting AF waveform following QRS subtraction was bandpass filtered using a 40 to 250 Hz second-order digital Butterworth filter. The absolute value of the filtered waveform was low-pass filtered using a 20 Hz second-order digital Butterworth filter. This filtering process extracts a time-varying waveform proportional to the amplitude of the high-frequency components in the original atrial EG, enhancing the periodicity or nonperiodicity of the signal. This algorithm was used to take a complex waveform and transform it to a series of atrial activations while diminishing the effects of changing EG morphology and/or amplitude (27).

An FFT was calculated on the digitally filtered waveform over a sliding 2-s window of 2,048 points every 0.5 s (Fig. 2). The data were tapered using a split cosine bell window. The largest peak of the resulting magnitude spectrum was identified and the position of the harmonic peaks was determined on the basis of its position. The areas under the largest peak and three of its harmonic peaks were each calculated over a 1-Hz window. This produced an area under four peaks. The total area of the spectrum was calculated from 2.5 Hz up to but not including the fifth harmonic peak. Higher frequencies were excluded because they were assumed to exceed the physiologic range of frequencies for AF wavelets. The ratio of the power under the harmonic peaks to the total power in this range was calculated, and the resulting number was defined as the OI. The OI was theorized to represent the organization of AF at that period in time. On the basis of previous experiments, an OI threshold of >0.5 was selected to represent times with relatively organized AF signals (19).

Burst pace termination protocol. Decapolar catheters, situated in the right and left atrial appendages, were used for burst pacing following the initiation of AF. For each AF episode, burst pace termination was attempted either at the RA appendage, the LA appendage, or biatrially by pacing through both decapolar catheters simultaneously. Burst pacing was performed with a cycle length of 50 ms, a pulse width of 9.9 ms, and an output of 9.9 mA. The burst pace duration was varied between 1 and 4 s. The burst pace was either delivered randomly or synchronized to an OI >0.5 . The duration of the burst pace, OI synchronization, and the pacing site were all randomized. A successful burst pace

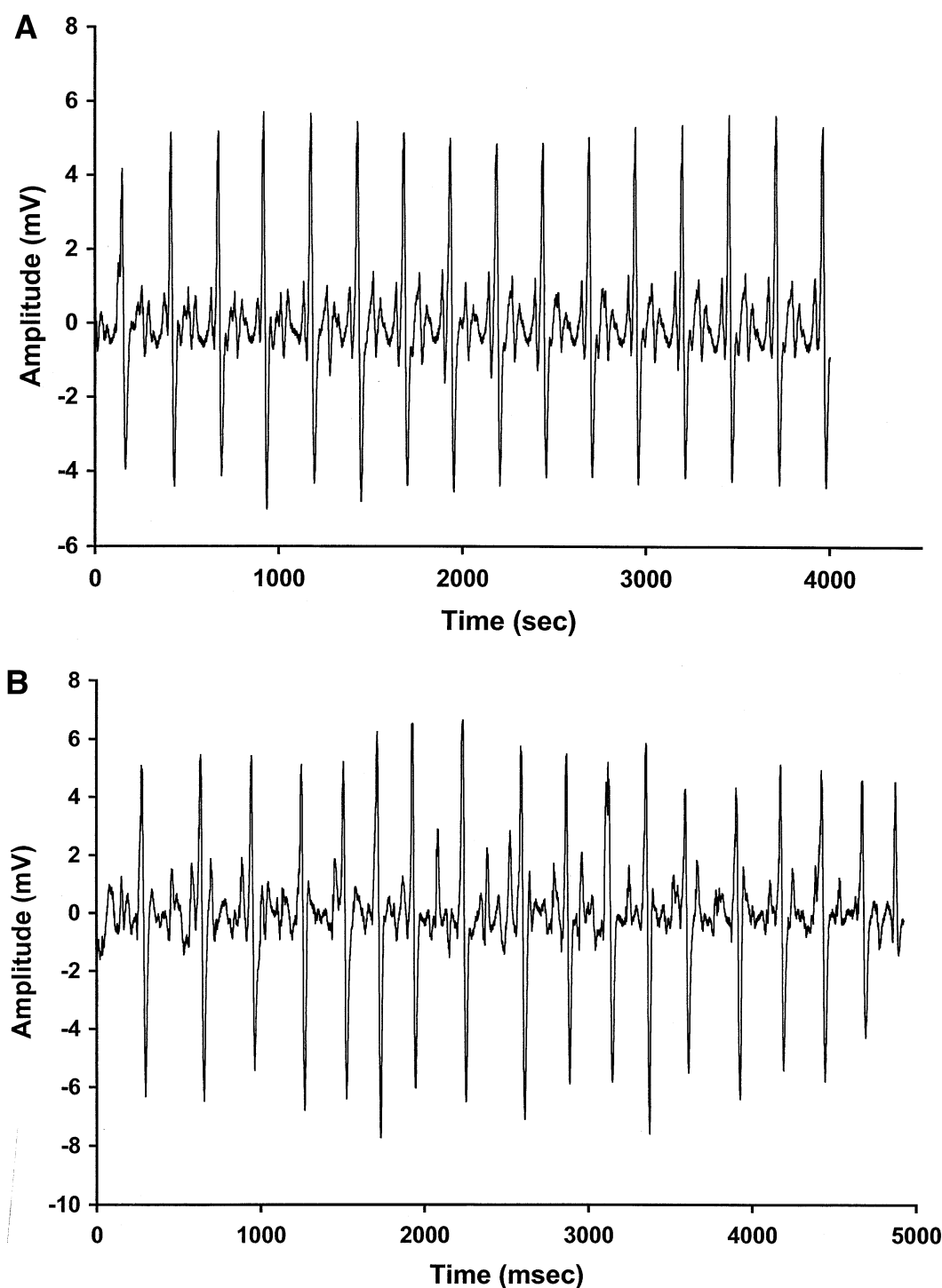


Figure 1. (A) A 4-s acquisition of an unfiltered wide bipolar electrogram from the coil electrodes placed in the left atrium and the right atrium. This signal was obtained just before a successful attempt to terminate atrial fibrillation (AF) through rapid burst atrial pacing. The high-amplitude activity represents the far-field ventricular activation, and the low-amplitude signal represents global bipolar interatrial activity. In this example, the AF signal is transiently very well organized (“flutterlike”), as evidenced by the regular 2:1 ventricular response to an atrial rhythm with a cycle length of 120 to 130 ms. (B) An unfiltered wide bipolar electrogram obtained from the same animal immediately before an unsuccessful attempt to terminate AF through rapid burst atrial pacing. The atrial activity and the ventricular response are grossly irregular, suggesting a more disorganized rhythm.

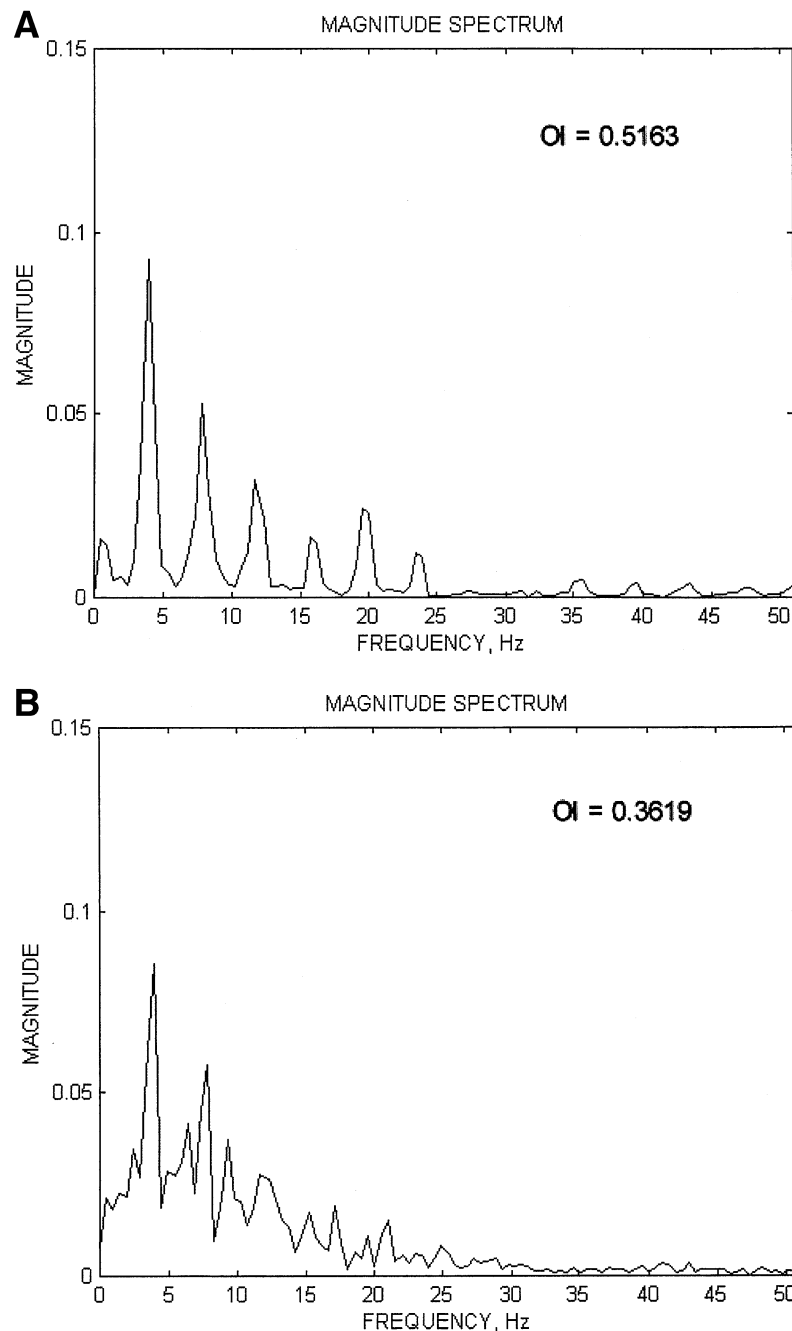


Figure 2. Results from a fast Fourier transform performed on the signals from Figure 1 after QRS subtraction and digital filtering. **Panel A** shows a dominant peak with discrete harmonics and little magnitude between the peaks. This resulted in a high (organized) organization index (OI) number. **Panel B** shows a high magnitude of spectral power between the harmonic peaks. This resulted in a low (disorganized) OI number.

termination was defined as AF termination within 3 s of the last burst pace stimulus. In all cases, burst pace termination of AF was attempted after spontaneous or induced AF of at least 30 s of sustained duration. If the AF terminated, it was reinitiated with 10-s burst of rapid atrial pacing as described above for further testing.

Statistical analysis. Data were expressed as the mean \pm SD or as a point estimate with 95% confidence intervals. The burst pace termination results were analyzed by generalized estimat-

ing equations by using a generalized linear model. The model parameters for the fixed effects were estimated by maximum likelihood, and the variance-covariance parameters were estimated by the Huber and White estimator. The log odds ratio was used as the statistic for hypothesis testing. Data were tested for normality using the Kolmogorov-Smirnov test. Statistical significance was defined as $p < 0.05$. All statistical computations were conducted in Splus 2000 (Insightful, Inc., Seattle, Washington).

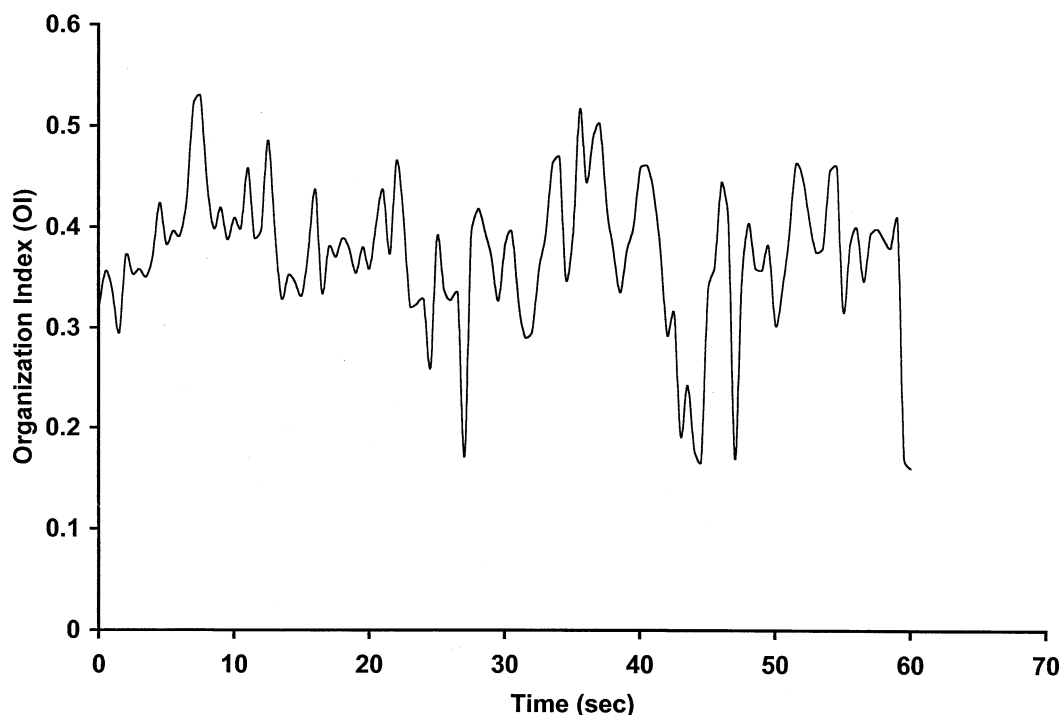


Figure 3. Calculated organization index (OI) values for a 1-min atrial fibrillation signal acquisition. A sliding 2-s window was used to calculate an OI every 0.5 s. A large variance in the OI is seen over time.

RESULTS

After the pacemaker was turned off, three of the nine dogs were in AF. In these animals, AF lasted for >10 min before spontaneous termination. In the remaining six dogs, AF was induced with a 10-s burst of rapid atrial pacing immediately after the pacemaker was turned off. In these six dogs, the duration of AF after the 10-s burst ranged from 45 s to 10 min (median 4.5 min) before spontaneous termination. Burst pace termination of AF was attempted 1,814 times and succeeded in seven of nine dogs. A total of 925 burst pace termination attempts were delivered randomly, and 889 burst pace termination attempts were synchronized to an OI >0.5. Termination of AF through burst pacing had an overall success rate of 11.1% for OI-synchronized attempts versus 6.3% for random attempts ($p < 0.0001$). For each animal, significant variability of the OI over time was observed (Fig. 3). In these nine animals, the OI was normally distributed (Fig. 4A) with a mean of 0.41 ± 0.11 , a maximum of 0.61 ± 0.09 , and a minimum of 0.19 ± 0.05 . In the two animals in which AF did not terminate with burst atrial pacing, the OI was lower on average than the OIs for the animals in which burst pace termination of AF was successful (0.36 ± 0.03 vs. 0.42 ± 0.08).

The distribution of OIs for all burst pace termination attempts synchronized to an OI >0.5 is shown in Figure 4, B, and demonstrated a distribution similar to the tail of the normal distribution for all OI measurements above the 0.5 threshold value. The prevalence of burst pace termination of AF with respect to pacing site and burst pace duration is shown in Figure 5. Biatrial pacing for 3 s synchronized to an

OI >0.5 had the highest success rate for terminating AF. The 97 trials for AF termination with this configuration were successful in 24 cases (24.7%). Overall, OI-synchronized biatrial pacing was successful in terminating AF in 16.5% of attempts versus 8.2% for random ($p < 0.0001$). Figure 6 shows an example of biatrial pacing for a duration of 2 s resulting in the termination of AF. Also demonstrated is the rapid pacing capturing both atria. For RA-only and LA-only pacing sites, OI-synchronized burst pace termination had an overall higher success rate than random attempts, but this increase did not reach statistical significance. Figure 7 shows an example of rapid pacing from a RA site for a duration of 2 s that was not successful in terminating AF. As demonstrated in this example, single atrial pacing frequently failed to capture the contralateral atrium. For all pacing protocols, the odds of a successful termination of atrial fibrillation doubled when the pace duration was >1 s ($p > 0.03$).

DISCUSSION

In the present study, it has been shown that AF can be successfully captured and terminated with rapid burst atrial pacing. The highest success rate occurred when the burst was delivered during periods of high measured AF organization with biatrial pacing for 3 s. It has been shown that the spatiotemporal organization of AF varies over time. Delivering shocks during increased levels of AF organization, as measured by the OI, has shown to increase cardioversion efficacy (19). When this methodology was applied in attempting to burst pace terminate AF, similar results were

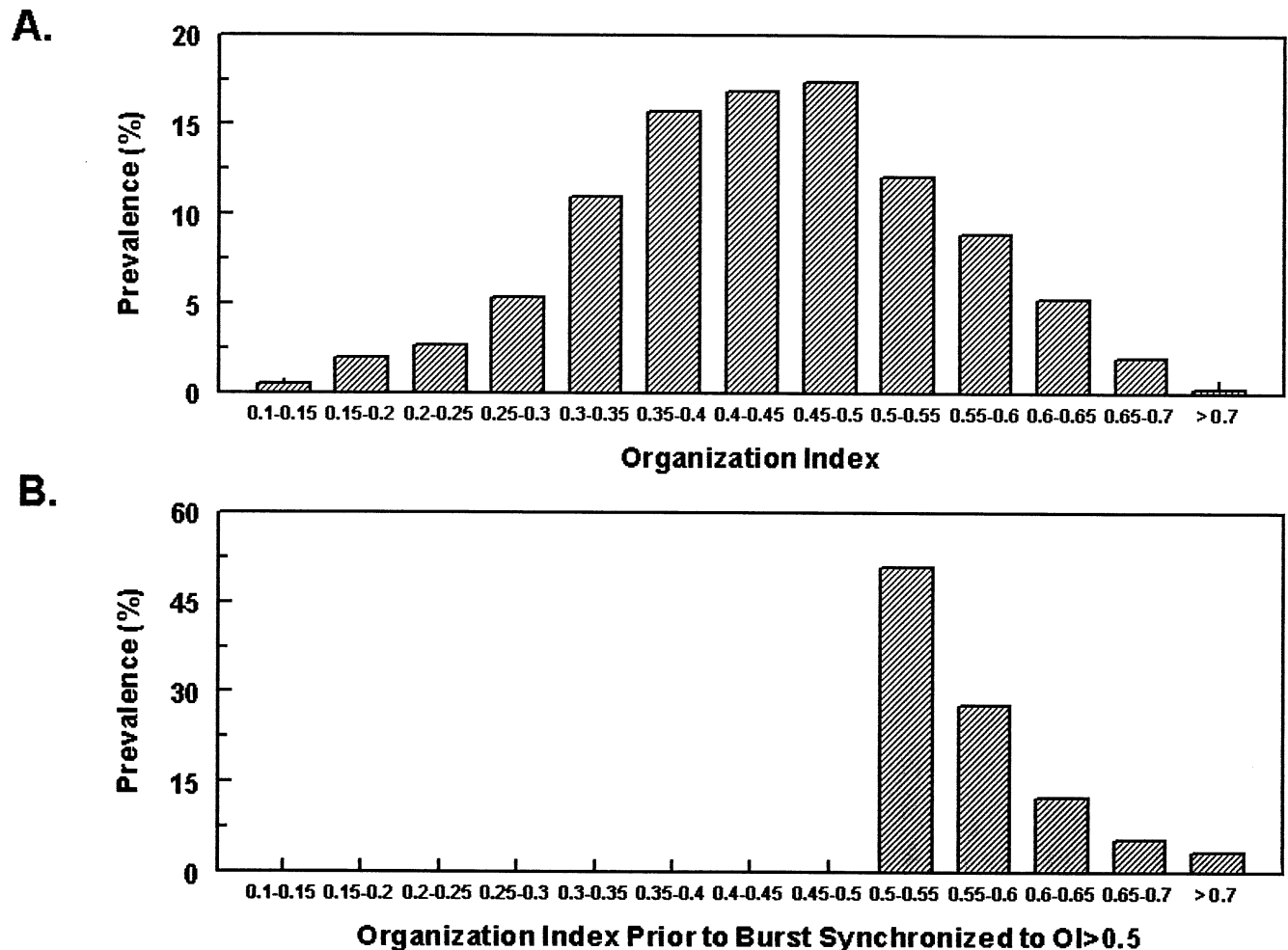


Figure 4. The distribution of organization indexes (OIs) calculated over a 60-s AF electrogram acquired from all nine animals is displayed in **panel A**. These data are normally distributed and are representative of the OI values at the time of randomly delivered rapid burst. **Panel B** shows the distribution of OI values recorded immediately before the burst pace termination attempts synchronized to OI values > 0.5 . By definition, the distribution curve is truncated at the 0.5 threshold value.

observed with increased efficacy of burst pace termination when the stimuli were synchronized to a high OI value.

It has been theorized that AF consists of multiple wavelets traveling through the atria (11,12,21). The number of wavelets circulating in the atria is inversely correlated to the regions of the excitable gap (15,28). Rapid burst pacing delivered outside the excitable gap has a lower chance of terminating AF because the tissue is refractory and the pacing will not capture a large enough mass of the atria to be effective. The burst must be delivered during periods of more “flutterlike” activity where an increased region of an excitable gap may exist and the atrial tissue is not refractory. The overdrive pacing could potentially produce regional atrial refractoriness and conduction block in regions of excitable gap, and possibly block the propagation of reentrant wavelets. The organization index may be able to identify these flutterlike periods during AF where a critical mass of atrial tissue is excitable, and allows for capture of the tissue and the possible termination of AF.

Previous Studies

Rapid atrial pacing. Several studies have shown that atrial flutter can be terminated with atrial overdrive pacing with varying success rates (1–10). Not until recently have studies looked at burst pacing during AF and the ability to regionally entrain AF for brief periods of time. Allesie *et al.* (11) showed that in a canine model, AF could be regionally controlled within a small pacing interval window, suggesting that an excitable gap may exist during AF. Kirchhoff *et al.* (12) took this study a step further by mapping the atria during rapid pacing in the presence of AF. The region of control of AF was shown to be activated by uniform wavefronts conducting away from the stimulation site until reaching intraatrial conduction block or colliding with other wavefronts (12). In humans, Daoud *et al.* (13) demonstrated that during type I AF, pacing the high right atrium can capture the RA and influence the signal in the LA. Two other studies by Capucci *et al.* and Kalman *et al.* (14,15) also demonstrated that regional entrainment of AF is possible by

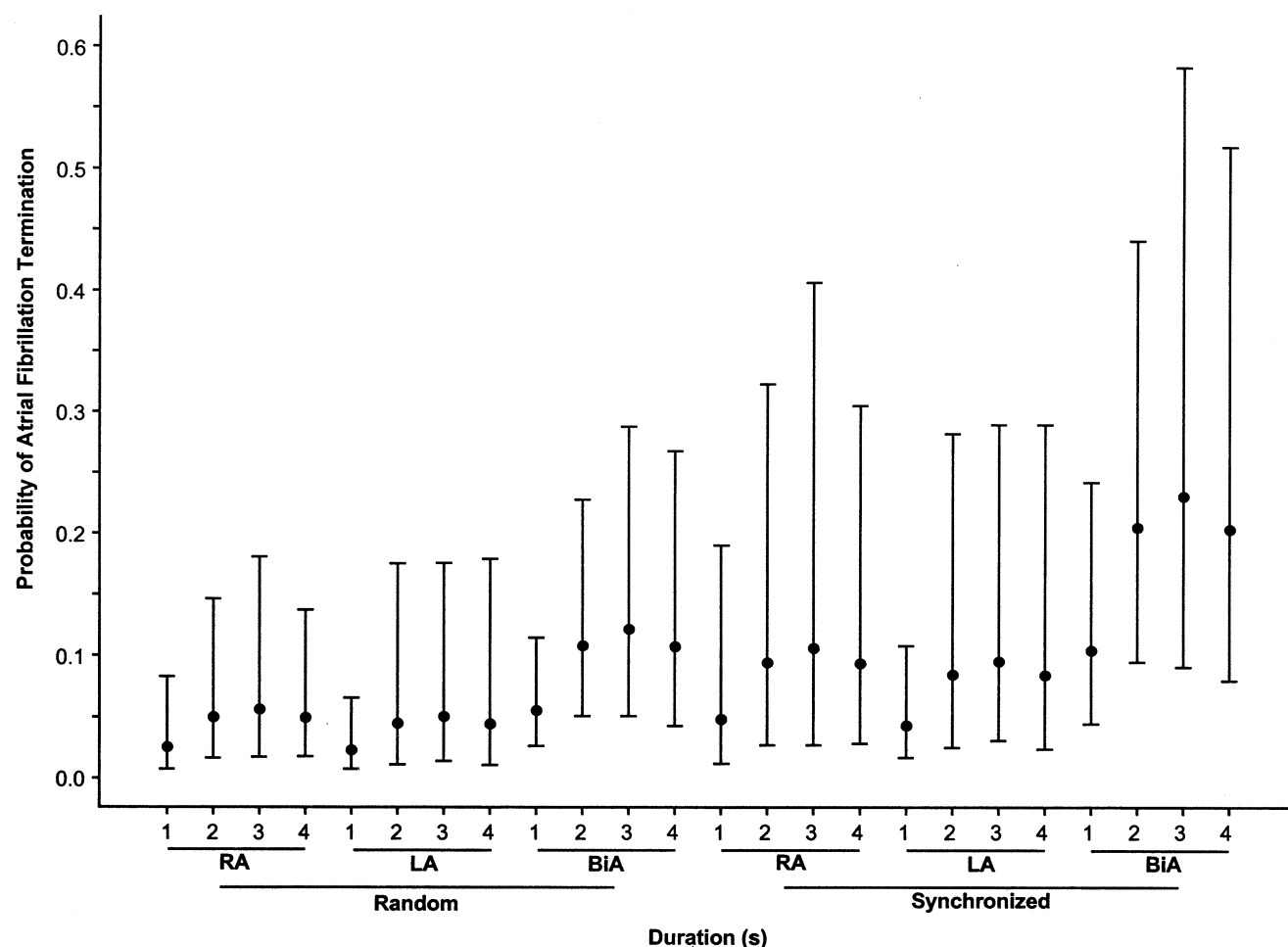


Figure 5. Success rates for the termination of atrial fibrillation (AF) with rapid burst pacing. Shown are the point estimates and the 95% confidence intervals for predicting the probability of a successful termination of AF. The results from each rapid pacing duration (1 to 4 s) are shown for pacing from the right atrium (RA), left atrium (LA), and biatrial pacing (BiA). A significant increase in the efficacy of the rapid atrial pacing for the termination of AF is seen with biatrial pacing synchronized to an organization index >0.5 . With this configuration, a 3-s rapid pacing window had the highest success rate (24.7%).

pacing the RA, suggesting that an excitable gap may be present during AF. All of these studies in both animals and humans look at the ability to regionally entrain AF; however, termination of AF during entrainment was not successful. The present study is the first to show that AF can be terminated with rapid atrial pacing.

Right and left atrium. The electrophysiologic differences between the RA and LA have been well documented (21–26). In animal models of AF, it has been shown that the LA has shorter atrial effective refractory periods and shorter AF cycle lengths than the RA (22). Sih *et al.* (21) demonstrated differences in activation maps between the RA and LA. Recently, it has also been shown that in a Langendorff-perfused sheep heart the LA has higher dominant frequencies during AF than the RA (26). These differences between the RA and LA with AF may play a role in whether pacing from an individual right atrial or left atrial bipole can capture both atria and terminate AF. This study demonstrates that the site of rapid pacing and the duration of the stimulus play major roles in the efficacy of termination of AF. Biatrial rapid burst atrial pacing proved to have a

higher success rate for terminating AF than pacing from the RA or LA alone.

Clinical implications. The present study shows that AF can be terminated with rapid burst atrial pacing. This may provide important therapeutic implications regarding the possibility of termination of paroxysmal AF without subjecting patients to painful shocks or the risks of anesthesia. This could be of particular importance for the atrial implantable defibrillator. A limitation for its use as a possible therapy for AF is shock-related discomfort (29–31). If a burst pace termination protocol were incorporated into the implantable atrial defibrillator as a first therapeutic option, AF might be terminated without the use of a painful shock and the risks that are associated with shock delivery.

Study limitations. This study was performed in a subacute AF model and it is unknown if this technique could be applied to a chronic AF model, or if human hearts would respond to this protocol in the same manner. A mechanism of reentry was presumed on the basis of prior mapping studies, but was not specifically confirmed in the present protocol. This animal model of AF may be analogous to

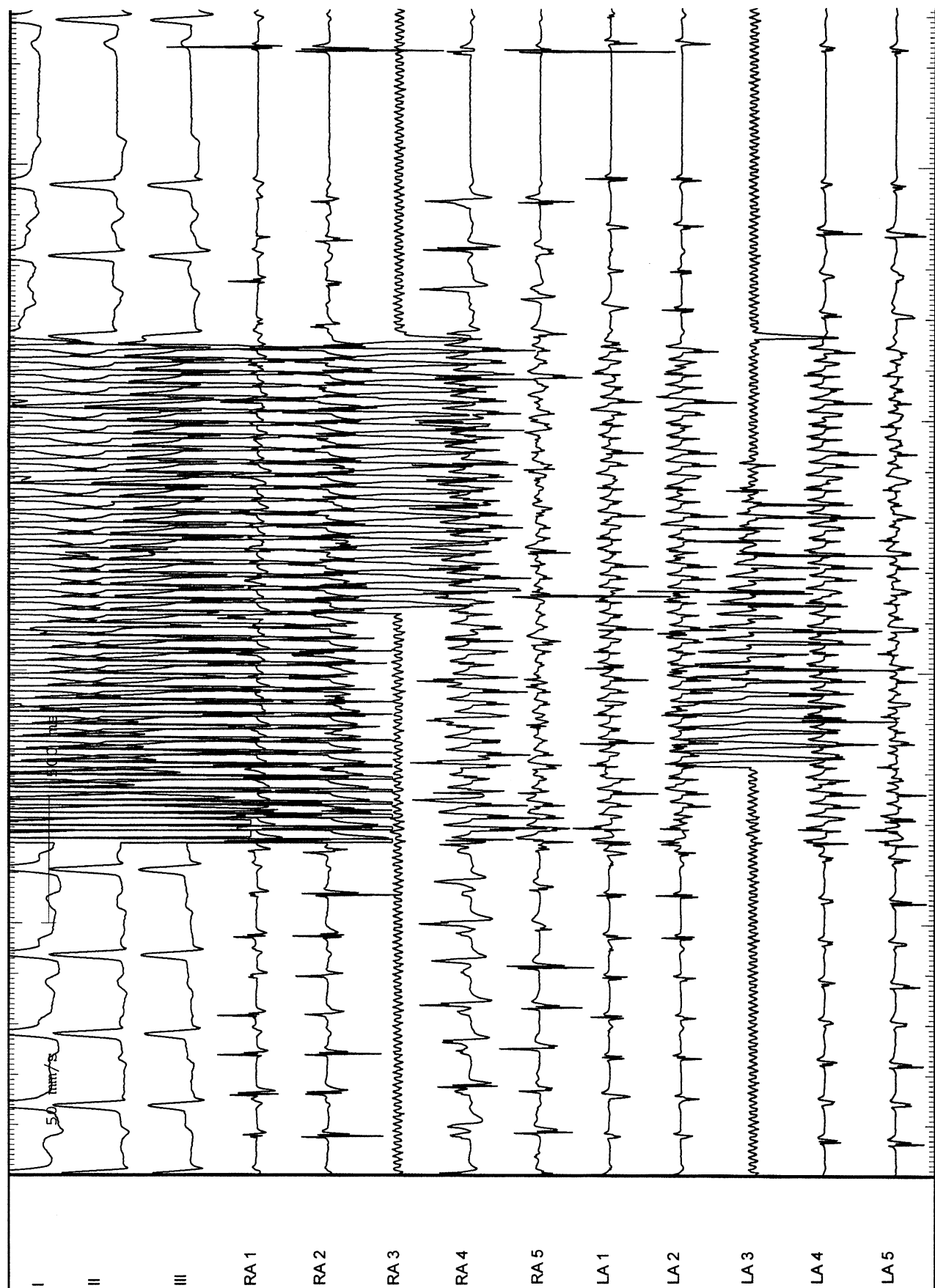


Figure 6. Electrograms from the decapolar catheters that were placed in the left atrium (LA) and the right atrium (RA). Biatrial rapid burst pacing for 2 s resulted in the termination of atrial fibrillation. During the pacing, both atria are captured. The channels labeled RA3 and LA3 were selected for pacing (pacing artifact during the pacing train is not uniformly displayed in the RA3 and LA3 channels because of limitations of the physiologic recorder software).

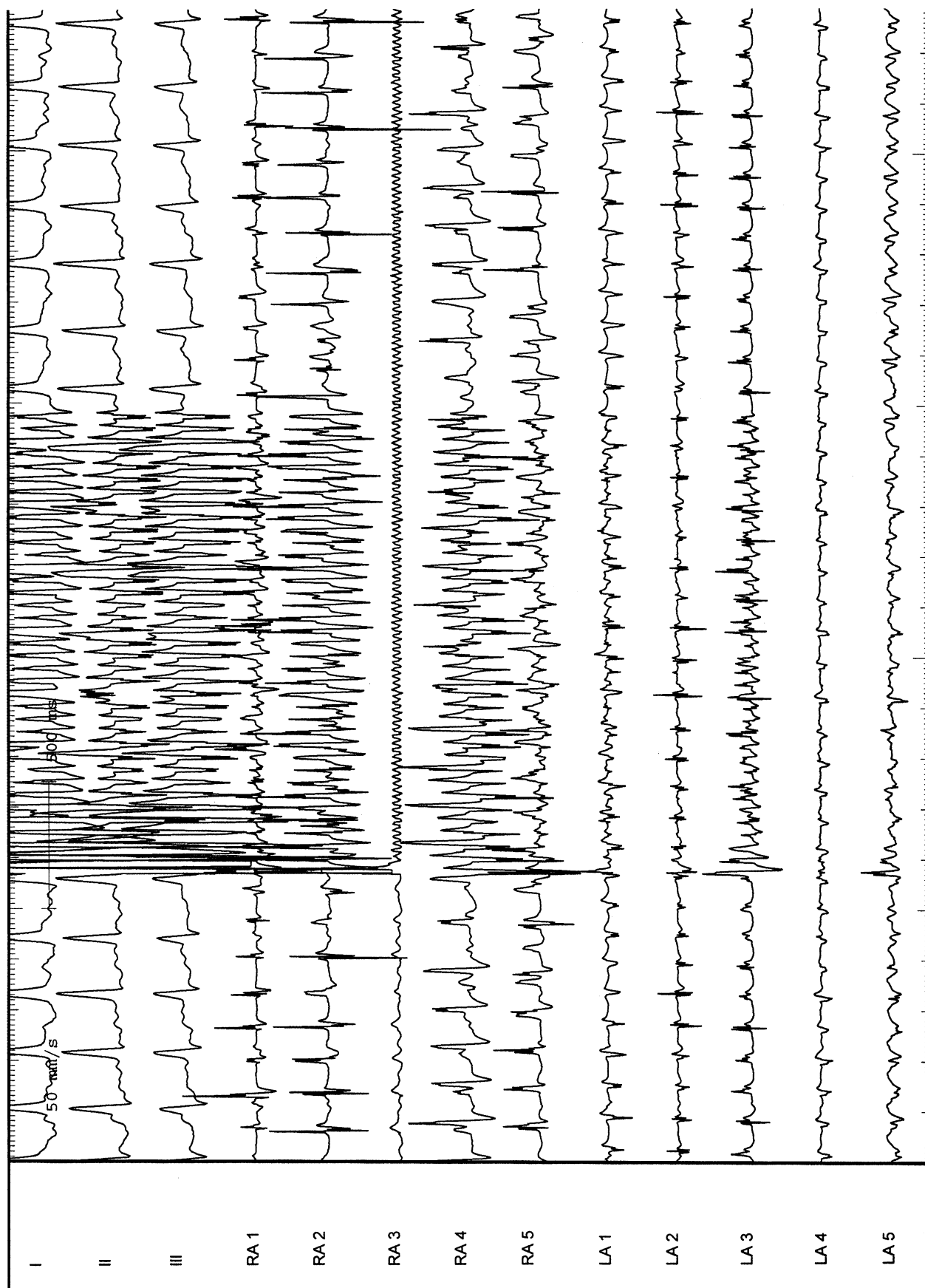


Figure 7. Electrograms from the decapolar catheters that were placed in the left atrium (LA) and the right atrium (RA). Right atrium rapid burst atrial pacing for 2 s did not terminate the atrial fibrillation. The LA electrograms showed no alterations in pattern or frequency in response to attempted burst pace termination from the RA. The channel labeled RA3 was selected for pacing (pacing artifact during the pacing train is not uniformly displayed in the RA3 channel because of limitations of the physiologic recorder software).

patients with AF of recent onset and brief duration. However, it is certainly not representative of patients with persistent or chronic AF. With persistent or chronic AF, it would be anticipated that the efficacy of burst pace termination would be lower.

The sites of burst pacing used in this study are different from what would be anticipated clinically because of the difficulty in accessing the coronary sinus in a closed-chest procedure in a canine. An RA-LA catheter placement was chosen instead of the RA-coronary sinus catheter placement that is used in human patients. We also cannot rule out the possibility of AF terminating and then reinitiating during the period of rapid pacing.

Conclusions. Using an algorithm that we developed to measure the organization of AF, we have shown that the organization of AF varies over time. By timing the delivery of burst pacing to time periods of increased measured AF organization, the efficacy of capture and termination of AF is improved. It also appears that biatrial pacing is more effective than pacing from the RA or the LA alone.

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